REMARKS

Prior to entry of the present amendment, claim 1-23 are pending. Claims 11-23, due to a restriction requirement, are withdrawn from consideration. Claims 9 and 10 are objected to and claims 1-10 are rejected under 37 C.F.R. § 103. Applicants address each of the bases for rejection as follows.

Claim Amendments

Claim 1 has been amended to recite the word "and" between steps (e) and (f), to incorporate the features of claim 2, and the correct a minor typographical error. In view of the amendment to claim 1, claim 2 has been canceled. Claims 9 and 10 have also been canceled. No new matter has been added by the present amendments.

Applicants reserve the right to pursue any canceled subject matter in this or in a continuing application.

Information Disclosure Statement

The Office objects to the GenBank references listed on the form PTO-1449 enclosed with the information disclosure statement filed on October 4, 2004 for not including a publication date. The form PTO-1449 submitted with the concurrently filed information disclosure statement includes dated GenBank entries. Applicants respectfully request consideration of the cited references.

Objection to the Specification

The Office states (pages 2 and 3):

> The specification contains sequence disclosures (e.g., page 101-103) that are encompassed by the definitions for nucleotide and/or amino acid sequences ... but are not present in the Sequence Listing and/or identified in the specification by sequence identifier numbers.

In response, Applicants direct the Office's attention to Applicants' September 23, 2004 reply to the Notice to File Missing Parts mailed on June 22, 2004. (For the Office's convenience, a copy of the September 23rd reply is enclosed.) In particular, Applicants note that, in the preliminary amendment filed with the September 23rd reply, the specification was amended to identify each nucleic acid or amino acid sequence (including those on pages 101-103 of the specification) by a unique sequence identifier. Applicants also filed a sequence listing in accordance with the requirements of 37 C.F.R. §§ 1.821-1.825 and the required sequence statement. Applicants submit that the specification, as amended in the September 23rd reply meets the sequence requirements of 37 C.F.R. §§ 1.821-1.825. This basis for objection may be withdrawn.

Objection to the Claims

Claims 9 and 10 are objected to based on the assertion that they fail to further limit the claim from which they depend. Claims 9 and 10 have been canceled. This basis for rejection, therefore, is moot.

Rejection under 35 U.S.C. § 103

Claims 1-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ahlert et al. (Cancer Res. 50:5962-5968, 1990; "Ahlert") as evidenced by Kroumpouzos et al. (Pigment Cell Res. 7:348-353, 1994; "Kroumpouzos"). Applicants respectfully submit that claim 1, as amended, and its dependent claims are free of this basis for rejection.

Claim 1, as amended, reads as follows.

> 1. A method of producing a tumor host range (T-HR) mutant virus, wherein said T-HR mutant virus is unable to propagate in normal cells, but is able to propagate in abnormally proliferating cells, said method comprising the steps of:
> (a) providing a wild-type viral DNA;
> (b) introducing random mutations in said wild-type viral DNA, thereby obtaining a collection of uncharacterized mutant viruses;
> (c) infecting *uncharacterized* abnormally proliferating cells with said collection of mutant viruses to amplify said mutant viruses;
> (d) selecting mutant viruses that have the ability to proliferate in said *uncharacterized* abnormally proliferating cells from said collection by plaque isolation;
> (e) infecting normally proliferating cells with mutant viruses selected in step (d); and
> (f) identifying mutant viruses from step (e) that do not proliferate in said normally proliferating cells, wherein said identified mutant viruses are identified as a T-HR mutant viruses. (Emphasis added.)

The specification, at page 17, lines 5-8, states:

> "Uncharacterized abnormally proliferating cell," as used herein, refers to a cell where *the cause of the abnormal proliferation is unknown.* For example, *the genetic alteration that results in abnormal proliferation has not been identified.* However, other features of the cell may be characterized. (Emphasis added.)

Applicants submit that neither Ahlert nor Kroumpouzos, alone or in combination, renders the presently claimed invention obvious.

Ahlert describes infecting abnormally proliferating MeWo cells with a collection of mutant viruses. The Office relies on Kroumpouzos for teaching that "MeWo cells do express an oncogene c-myc, and lost the biologically active tumor suppressor protein p53." While the Office apparently asserts that the cause of abnormal proliferation of MeWo cells is unknown, Applicants submit that the description in Kroumpouzos clearly indicates that genetic alterations that result in abnormal proliferation of MeWo cells have been identified. In particular, Table 1 of Kroumpouzos describes MeWo cells as lacking expression of the p53 tumor suppressor while expressing the *c-myc* oncogene. In view of Kroumpouzos, Applicants submit that Ahlert fails to teach or suggest using *uncharacterized* abnormally proliferating cells in a method of producing a virus that is unable to propagate in the uncharacterized abnormally proliferating cells.

To establish a *prima facie* case of obviousness under § 103, the Office must demonstrate that the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art. 35 U.S.C. § 103(a) (Supp. III 1997); *In re Dembiczak*, 175 F.3d 994, 998, 50 U.S.P.Q.2d 1614, 1616 (Fed. Cir. 1999), *abrogated on other grounds by In re Gartside*, 203 F.3d 1305, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). In the present case, the references, even if combined, fail to teach or suggest all of the

elements of the presently claimed invention. In particular, the references fail to teach or suggest infecting *uncharacterized* abnormally proliferating cells with a collection of mutant viruses. Applicants submit that the cited references fail to establish a *prima facie* case of obviousness for claim 1 and its dependent claims. The 35 U.S.C. § 103 rejection of claims 1 and 3-8 should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three (3) months, to and including April 5, 2007, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: April 4, 2007

Kristina Bieker-Brady, Ph.D.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

COPY

PATENT
ATTORNEY DOCKET NO. 00742/062004

Certificate of Mailing: Date of Deposit: September 21, 2004

I hereby certify under 37 C.F.R. § 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Janet D'Annunzio-Ellis
Printed name of person mailing correspondence

Janet D'Annunzio-Ellis
Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Thomas L. Benjamin	Art Unit:	1632
Serial No.:	10/828,815	Examiner:	Not Assigned
Filed:	April 21, 2004	Customer No.:	21559
Title:	DIAGNOSING AND TREATING CANCER CELLS USING MUTANT VIRUSES		

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136, Applicant hereby petitions that the period for replying to the Notice to File Missing Parts of Application that was mailed in connection with the above-captioned application on June 22, 2004 be extended for one (1) month, to and including September 22, 2004.

09/24/2004 MMEKONEN 00000138 10828815
02 FC:2251 55.00 OP

COPY

Enclosed is a check for $55.00 for the fee required by 37 C.F.R. § 1.17(a). If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 20, 2004

Kristina Bieker-Brady, Ph.D., P.C.
Reg. No. 39,109

Clark & Elbing LLP
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Janet D'Annunzio-Ellis
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Janet D'Annunzio-Ellis
Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Thomas L. Benjamin	Art Unit:	1632
Serial No.:	10/828,815	Examiner:	Not Assigned
Filed:	April 21, 2004	Customer No.:	21559
Title:	DIAGNOSING AND TREATING CANCER CELLS USING MUTANT VIRUSES		

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO NOTICE TO FILE MISSING PARTS OF APPLICATION

In reply to the Notice to File Missing Parts of Application that was mailed in connection with the above-captioned application on June 22, 2004, a copy of which is enclosed, Applicant, as a small entity, submits herewith the following:

- A Combined Declaration and Power of Attorney in compliance with 37 C.F.R. § 1.63.
- Payment of the surcharge of $65.00 for late filing of the declaration.
- A Sequence Listing and diskette.
- A Sequence Statement.

- A Preliminary Amendment.
- One Replacement Drawing.
- Petition for Extension of Time of one (1) Month with check for the $55.00 extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 10, 2004

Kristina Bieker-Brady, Ph.D., P.C.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/828,815	04/21/2004	Thomas L. Benjamin	00742/062004

CONFIRMATION NO. 7702

21559
CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

FORMALITIES LETTER

OC000000013008081

Date Mailed: 06/22/2004

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

09/24/2004 MMEKONEN 00000138 10828815

01 FC:2051 65.00 OP

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is unsigned.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

- This application clearly fails to comply with the requirements of 37 CFR. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper or compact disc copy of the "Sequence Listing", as well as an amendment directing its entry into the application. Applicant must also provide a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If applicant desires the sequence listing in the instant application to be identical with that of another application on file in the U.S. Patent and Trademark Office, such request in accordance with 37 CFR 1.821(e) may be submitted in lieu of a new CRF.

For questions regarding compliance to these requirements, please contact:

- **For Rules Interpretation, call (703) 308-4216**
- **To Purchase PatentIn Software, call (703) 306-2600**

- **For PatentIn Software Program Help, call (703) 306-4119 or e-mail at patin21help@uspto.gov or patin3help@uspto.gov**

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$65** for a Small Entity

- **$65** Late oath or declaration Surcharge.

Replies should be mailed to: Mail Stop Missing Parts
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P.O. Box 1450
Alexandria VA 22313-1450

A copy of this notice MUST be returned with the reply.

B.H.

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

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PATENT
ATTORNEY DOCKET NO. 00742/062004

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled **DIAGNOSING AND TREATING CANCER CELLS USING MUTANT VIRUSES**, the specification of which was filed on April 21, 2004 as Application Serial No. 10/828,815.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with 37 C.F.R. § 1.56.

FOREIGN PRIORITY RIGHTS: I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or (f), or § 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below, and have also identified below any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Country	Serial Number	Filing Date	Priority Claimed?
			Yes/No

PROVISIONAL PRIORITY RIGHTS: I hereby claim priority benefits under 35 U.S.C. § 119(e) of any United States provisional patent application(s) listed below filed by an inventor or inventors on the same subject matter as the present application and having a filing date before that of the application(s) of which priority is claimed:

Serial Number	Filing Date	Status
60/339,140	December 10, 2001	Abandoned
60/216,723	July 7, 2000	Abandoned

NON-PROVISIONAL PRIORITY RIGHTS: I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Serial Number	Filing Date	Status
10/765,520	January 27, 2004	Pending

COPY

Serial Number	Filing Date	Status
10/316,532	December 10, 2002	Pending
09/988,117	November 16, 2001	Abandoned
09/812,471	March 19, 2001	Abandoned
09/812,633	March 19, 2001	Abandoned

I hereby appoint the attorneys and/or agents associated with customer number **21559** to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Address all correspondence relating to this application to the address associated with customer number **21559**, which is Clark & Elbing LLP, 101 Federal Street, Boston, MA 02110.

Address all telephone calls to: Kristina Bieker-Brady, Ph.D. at 617-428-0200.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Full Name (First, Middle, Last)	Residence Address (City, State, Country)	Post Office Address (Street, City, State, Country)	Citizenship
Thomas L. Benjamin	Cambridge, MA U.S.A.	595 Putnam Avenue Cambridge, MA 02139	United States
Signature:			Date: 6/24/04

PATENT
ATTORNEY DOCKET NO. 00742/062004

Certificate of Mailing: Date of Deposit: September 21, 2004

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Janet D'Annunzio-Ellis
Printed name of person mailing correspondence

Janet D'Annunzio-Ellis
Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Thomas L. Benjamin	Art Unit:	1632
Serial No.:	10/828,815	Examiner:	Not Assigned
Filed:	April 21, 2004	Customer No.:	21559
Title:	DIAGNOSING AND TREATING CANCER CELLS USING MUTANT VIRUSES		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Prior to examination of the above-captioned application, kindly amend the application as follows.

AMENDMENTS TO THE SPECIFICATION:

Insert the sequence listing submitted with the concurrently filed Statement under 37 C.F.R. §§ 1.821-1.825 at the end of the specification.

Amend the paragraph beginning on page 10, line 6, as follows.

In another aspect, the invention features an isolated nucleic acid encoding a Death Inducer with SAP Domain amino acid sequence, where this Death Inducer with SAP Domain amino acid sequence is at least 30% identical to the amino acid sequence of ~~SEQ ID NO:2~~ SEQ ID NO:33 or ~~SEQ ID NO: 4~~ SEQ ID NO:35 and induces DNA condensation and apoptosis in a mammalian cell. However, this Death Inducer with SAP Domain amino acid sequence may also include the amino acid sequence of ~~SEQ ID NO: 2~~ SEQ ID NO:33 or ~~SEQ ID NO: 4~~ SEQ ID NO:35. In addition, the nucleic acid encoding the Death Inducer with SAP Domain amino acid may include the nucleic acid sequence of ~~SEQ ID NO:1~~ SEQ ID NO:32 or ~~SEQ ID NO:3~~ SEQ ID NO:34.

Amend the paragraph beginning on page 10, line 15, as follows.

In yet another aspect, the invention features a method of killing an abnormally proliferating cell. This method involves contacting the abnormally proliferating cell with a *Death Inducer with SAP Domain* nucleic acid sequence, where this contacting results in the expression of a DIS polypeptide in the abnormally proliferating cell. The *Death Inducer with SAP Domain* nucleic acid sequence may include, for example, the nucleic acid sequence of ~~SEQ ID NO:1~~ SEQ ID NO:32 or ~~SEQ ID NO:3~~ SEQ ID NO:34. In

addition, the abnormally proliferating cell may be an endometrial, prostate, or ovarian cell.

Amend the paragraph beginning on page 11, line 12, as follows.

In yet another aspect, the invention features a method of decreasing virus, for example, tumor virus, replication and dissemination. This method includes the step of contacting a cell infected with a virus with a T-HR mutant target gene nucleic acid sequence, where this contacting results in the expression of a T-HR mutant target gene encoded polypeptide in the cell infected with the virus and prevents the virus from replicating and disseminating, or, for instance, from replicating or disseminating. For example, the virus may be a DNA tumor virus. In addition, in desirable embodiments, the T-HR mutant target gene nucleic acid sequence may be a *Taz*, a *GAP SH3 binding protein*, a *nucleolin*, a *Vesicle Associated Protein 1,* or a *Death Inducer with SAP Domain* nucleic acid sequence, such as the *Death Inducer with SAP Domain* nucleic acid sequence of ~~SEQ ID NO:1~~ SEQ ID NO:32 or ~~SEQ ID NO:3~~ SEQ ID NO:34.

Amend the paragraph beginning on page 22, line 14, as follows.

By a "*DIS* nucleic acid sequence" or "*Death Inducer with SAP domain* nucleic acid sequence," as used herein is meant a nucleic acid sequence that is at least 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to a nucleic acid sequence provided of ~~SEQ ID NO:1~~ SEQ ID NO:32 or ~~SEQ ID NO:3~~ SEQ ID NO:34 over a region comprising at least 200, 300, 500, 750, 1000, 1500, 2000, 2500, 3000, or 3500 contiguous

nucleotides. In addition, a "*DIS* nucleic acid sequence" may be identical to the nucleic acid sequence of ~~SEQ ID NO:1~~ SEQ ID NO:32 or ~~SEQ ID NO:3~~ SEQ ID NO:34. In desirable embodiments, a "*DIS* nucleic acid sequence" is a human or a mouse *DIS* nucleic acid sequence that is at least 75%, 80%, 85%, 90%, or 95% identical to the human *DIS* nucleic acid sequence of ~~SEQ ID NO:3~~ SEQ ID NO:34, or to the murine *DIS* nucleic acid sequence of ~~SEQ ID NO:1~~ SEQ ID NO:32, over a region encompassing at least 1000, 2000, 3000, or 3500 contiguous nucleotides, and encodes a protein which induces DNA condensation and apoptosis in mammalian cells.

Amend the paragraph beginning on page 22, line 27, as follows.

By a "DIS polypeptide," a "Death Inducer with SAP domain polypeptide," a "DIS amino acid sequence," or a "Death Inducer with SAP domain amino acid sequence," as used herein is meant an amino acid sequence that is at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical to the amino acid sequence of ~~SEQ ID NO:2~~ SEQ ID NO:33 or ~~SEQ ID NO:4~~ SEQ ID NO:35 over a region comprising at least 50, 75, 100, 200, 300, 500, 700, 900, or 1200 contiguous amino acids. In addition, a "DIS polypeptide" may be identical to the amino acid sequence of ~~SEQ ID NO: 2~~ SEQ ID NO:33 or ~~SEQ ID NO: 4~~ SEQ ID NO:35. In desirable embodiments, a "Death Inducer with SAP domain (DIS) polypeptide" or a "Death Inducer with SAP domain (DIS) amino acid sequence" is a human or a mouse DIS polypeptide or amino acid sequence that is at least 30%, 50%, 60%, 70%, 80%, 90%, or 95% identical to the human DIS amino acid sequence of ~~SEQ ID NO: 4~~ SEQ ID NO:35, or the mouse DIS amino acid sequence of

~~SEQ ID NO: 2~~ SEQ ID NO:33, over a region encompassing 500, 700, 900, or 1200 contiguous amino acids, and induces DNA condensation and apoptosis in mammalian cells.

Amend the paragraph beginning on page 30, line 14, as follows.

Fig. 2A is sequence comparison between a region of the wild-type and TMD25 polyoma virus large T antigen nucleic acid and amino acid sequences and shows the 20 bp sequence duplication responsible for the TMD25 mutation (SEQ ID NOS:9-12).

Amend the paragraph beginning on page 30, line 21, as follows.

Fig. 2C is a series of large T antigen amino acid sequences and shows the deletion analysis of the TMD25 mutant (SEQ ID NOS:13-21).

Amend the paragraph beginning on page 32, line 22, as follows.

~~Fig. 22~~Figs. 22A-22E ~~is~~ are the sense (~~SEQ ID NO:1~~ SEQ ID NO:32) and the antisense strand of the murine *DIS* nucleic acid sequence as well as the corresponding amino acid sequence (~~SEQ ID NO:2~~ SEQ ID NOS:33 and 36-45).

Amend the paragraph beginning on page 32, line 25, as follows.

~~Fig. 23~~Figs. 23A and 23B ~~is~~ are the murine *DIS* nucleic acid sequence (~~SEQ ID NO: 1~~ SEQ ID NO:32).

Amend the paragraph beginning on page 32, line 26, as follows.

~~Fig. 24~~Figs. 24A-24E ~~is~~ are the murine *DIS* nucleic acid sequence (~~SEQ ID NO: 1~~ SEQ ID NO:32) and the amino acid sequence encoded by the open reading frame of murine DIS (~~SEQ ID NO: 2~~ SEQ ID NO:33).

Amend the paragraph beginning on page 33, line 1, as follows.

~~Fig. 25~~Figs. 25A-25E ~~is~~ are the sense (~~SEQ ID NO: 3~~ SEQ ID NO:34) and the antisense strand human *DIS* nucleic acid sequence as well as the corresponding amino acid sequence (~~SEQ ID NO:4~~ SEQ ID NOS:35 and 46-53).

Amend the paragraph beginning on page 33, line 4, as follows.

~~Fig. 26~~Figs. 26A and 26B ~~is~~ are the human *DIS* nucleic acid sequence (~~SEQ ID NO: 3~~ SEQ ID NO:34).

Amend the paragraph beginning on page 33, line 5, as follows.

~~Fig. 27~~Figs. 27A-27D ~~is~~ are the human *DIS* nucleic acid sequence (~~SEQ ID NO: 3~~ SEQ ID NO:34) and the amino acid sequence encoded by the open reading frame of human DIS (~~SEQ ID NO: 4~~ SEQ ID NO:35).

Amend the paragraph beginning on page 33, line 16, as follows.

~~Fig. 32~~Figs. 32A and 32B ~~is~~ are a series of Western blots showing that DIS, PARP, and LaminB are cleaved in BMK and HeLa cells upon induction of apoptosis by

staurosporine (A), and that caspase-3 and caspase-8 inhibitors can inhibit DIS cleavage (B).

Amend the paragraph beginning on page 47, line 27, as follows.

Furthermore, when we induced apoptosis in BMK and HeLa cells with staurosporine, we observed that DIS was degraded and that PARP and LaminB were cleaved (Fig. 32, panel A). Both PARP and LaminB are cleaved by caspases during apoptosis. We also observed that caspase-3 and caspase-8 inhibitors inhibited cleavage of DIS (Fig. 32, panel B). In view of these results, we analyzed the structure of human and mouse DIS and identified a number of caspase-3 and caspase-8 cleavage sites (Fig. 33). *In vitro* caspase cleavage experiments showed that DIS is sensitive to caspase-3 and that the first caspase-3 site (at amino acid 691 in human DIS (~~SEQ ID NO: 4~~ SEQ ID NO:35) and amino acid 689 in murine DIS (~~SEQ ID NO: 2~~ SEQ ID NO:33)) is used for cleavage (Fig. 34). Consequently, DIS is likely to function in regulating apoptosis and may be used in methods to diagnose and treat proliferative disorders.

Amend the paragraph beginning on page 71, line 23, as follows.

We generated TAZ knock out mice by replacing exon 2 (which encodes amino acids 1-144 of murine DIS; ~~SEQ ID NO: 2~~ SEQ ID NO:33) of the mouse TAZ gene with the pSAbeta-galpGKneopGKdta positive-negative selection vector (Figure 35). The TAZ knock out construct was transfected into an Embryonic Stem (ES) cell line and two positive ES clones were obtained and confirmed by PCR and by Southern blot. A

Southern blot for the *neo* gene also confirmed that only exon 2 of TAZ was replaced. We performed microinjections with these ES clones and obtained chimeric mice. Nine F1 $TAZ^{+/-}$ mice were obtained from different chimeric mice and these mice were mated to each other to generate $TAZ^{-/-}$ knockout mice.

Amend the paragraph beginning on page 101, line 25, as follows.

Total RNAs from SK-Vector and SK-P150 clones were amplified using primer pairs (5'-CGT CAC CTG AGG TGA CAC AGC AAA GC-3' (SEQ ID NO:22) and 5'-CGC TTC CAG GAC TGC AGG CTT CCT G-3' (SEQ ID NO:23). G3PDH was amplified using (5'-CAG ACC CCA AAT CTG CAG ATA CTC AG-3' (SEQ ID NO:24) and 5'-CAC TGG AAT TGG AAC TCT TCT GTC GAG-3' (SEQ ID NO:25)). Amplification mixtures from cycle numbers with linear amplification were used for comparing relative quantities of transcripts. Amplified G3PDH cDNA was used as an internal control to normalize the amount of p21 cDNA. The ratio of p21 versus G3PDH is the average of three linear amplification cycles.

Amend the paragraph beginning on page 102, line 22, as follows.

ChIP was performed as described previously by Weinmann et al., Methods 26:37-47, 2003). P19 cells extracts were used for ChIP. Chromatin elute was amplified using mouse p21 promoter specific primers: 5'-GAA GTA GGA GTC ACC GTC CTG TTT ACC-3' (SEQ ID NO:26) and 5'-GAT GTC TCT GTA TAG CCC TGG CTG TC-3' (SEQ ID NO:27) for 45 cycles. As a non-specific control, GAPD (glyceraldehyde-3-

phosphate dehydrogenase) gene was amplified with 5'-GCT GAA CGG GAA GCT CAC TGG CAT GG-3' (SEQ ID NO:28) and 5'-GAG GTC CAC CAC CCT GTT GCT GTA GC-3' (SEQ ID NO:29).

Amend the paragraph beginning on page 103, line 2, as follows.

Two p150 specific siRNA duplexes were made (Dharmacon Research, CO) 5'-AAG GAG AUG GAC AGU AAU GAG-3' (SEQ ID NO:30) and 5'-AAC CCC AUU ACC UCC AGA AUC-3' (SEQ ID NO:31) and transfected together into HOSE cells using Oligofectamine (Invitrogen) follow manufacturer's suggestions. The cells were serum-starved (0.2% serum) for 48 hrs and stimulated with 10% FBS and 100 uM BrdU. After 18hrs, cells were fixed and stained for BrdU and DAPI. p21 was detected by immunoprecipitation followed by Western blot. P150 and tubulin were detected directly by Western blot.

AMENDMENTS TO THE DRAWINGS:

Please amend drawing sheet 28 of 54 to be labeled Fig. 24E.

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REMARKS

Applicant has amended the specification to refer to each nucleic acid or amino acid sequence by a sequence identification number.

Applicant also corrects a typographical error in the labeling of Figure 24E. As required under 37 C.F.R. § 1.121(d), enclosed is a corrected drawing which, in the header, is labeled "Replacement Sheet." On this Replacement Sheet the labeling has been changed from "Fig. 13E" to "Fig. 24E." No new matter has been added by these amendments.

Enclosed, with the concurrently filed reply to Notice to File Missing Parts, are a petition to extend the period for replying to the Notice by one month, to and including September 22, 2004, and a check in the amount of the required fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 20, 2004

Kristina Bieker-Brady, Ph.D., P.C.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

FIG. 24E

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Certificate of Mailing: Date of Deposit: September 21, 2004

I hereby certify under 37 C.F.R. § 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Janet D'Annunzio-Ellis
Printed name of person mailing correspondence

Janet D'Annunzio-Ellis
Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Thomas L. Benjamin	Art Unit:	1632
Serial No.:	10/828,815	Examiner:	Not Assigned
Filed:	April 21, 2004	Customer No.:	21559
Title:	DIAGNOSING AND TREATING CANCER CELLS USING MUTANT VIRUSES		

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT UNDER 37 C.F.R. §§ 1.821-1.825

In reply to the Notice to File Missing Parts of a Nonprovisional Application that was mailed in connection with the above-captioned application on June 22, 2004, enclosed is a Sequence Listing in accordance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 and consisting of 28 pages.

As required by 37 C.F.R. § 1.821(c), the Sequence Listing appears as a separate part of the application. Each sequence in the application appears separately in the

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Sequence Listing, and each sequence in the Sequence Listing is assigned a separate sequence identifier.

As required by 37 C.F.R. § 1.821(d), the sequence identifiers are used throughout the application description and claims to refer to their respective sequences.

As required by 37 C.F.R. § 1.821(e), enclosed is a diskette containing a copy of the Sequence Listing in computer readable form.

As required by 37 C.F.R. § 1.821(f), I hereby state that the contents of the computer readable form of the Sequence Listing are the same as the contents of the paper copy.

As required by 37 C.F.R. § 1.821(g), I hereby state that this submission contains no new matter.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 20, 2004

Kristina Bieker-Brady, Ph.D., P.C.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

SEQUENCE LISTING

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Using Mutant Viruses

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Gly Gly Gln Glu Asn Pro Ser Asn Ser Ser Ala Ser Ser Ala Pro Arg
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Pro Glu Gly His Ser Arg Ser Gln Val Met Asp Thr Glu His Ser Asn
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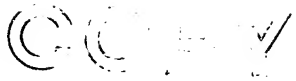

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Lys Leu Gln Leu Leu Glu Glu Lys Thr Asp Glu Asp Gly Lys Thr Ile
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465                 470                 475                 480
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Glu Thr His Lys Gly Arg Thr Val Pro Ala His Val Glu Thr Val Val
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705                 710                 715                 720
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785                 790                 795                 800
Gln Arg Asp Phe Gly Val Arg Ile Tyr Lys Ser Leu Leu Ser Leu Pro
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Tyr Leu Leu Glu Lys Asp Leu Glu Glu Ile Leu Tyr Thr Leu Gly Leu
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Arg Glu Ser Cys Phe Tyr Arg Lys Leu Thr Asp Thr Ser Lys Asp Glu
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Ile Arg Asn Leu Ser Thr Val Met Asp Glu Ile His Thr Val Leu Lys
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<400> 37
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<210> 38
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Collette R. D'Amico
Printed name of person mailing correspondence

Collette R. D'Amico
Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Thomas L. Benjamin	Confirmation No.	7702
Serial No.:	10/828,815	Art Unit:	1633
Filed:	April 21, 2004	Examiner:	Q. J. Li
Customer No.:	21559		
Title:	DIAGNOSING AND TREATING CANCER CELLS USING MUTANT VIRUSES		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Applicant submits the references listed on the enclosed Form PTO-1449, copies of which are enclosed.

This statement is being filed after a first Office Action on the merits, but before the mailing of a final Office Action or a Notice of Allowance. A check for $180.00 in payment of the fee set forth in 37 C.F.R. § 1.17(p) is enclosed.

Submission of this statement is not a representation that a search has been made, nor is the inclusion of information in this statement an admission that the information is

material to patentability.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: April 4, 2007

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Reg. No. 39,109

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